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Febrile seizures: an appropriate-aged model suitable for long-term studies

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Abstract

Seizures induced by fever are the most prevalent age-specific seizures in infants and young children. Whether they result in long-term sequelae such as neuronal loss and temporal lobe epilepsy is controversial. Prospective studies of human febrile seizures have found no adverse effects on the developing brain. However, adults with temporal lobe epilepsy and associated limbic cell loss frequently have a history of prolonged febrile seizures in early life. These critical issues may be resolved using appropriate animal models. Published models of hyperthermic seizures have used ‘adolescent’ and older rats, have yielded a low percentage of animals with actual seizures, or have suffered from a high mortality, rendering them unsuitable for long-term studies. This article describes the establishment of a model of febrile seizures using the infant rat. Hyperthermia was induced by a regulated stream of mildly heated air, and the seizures were determined by both behavioral and electroencephalographic (EEG) criteria. Stereotyped seizures were generated in 93.6% of 10–11-day-old rats. EEG correlates of these; seizures were not evident in cortical recordings, but were clearly present in depth recordings from the amygdala and hippocampus. Prolonged febrile seizures could be induced without burns, yielding a low mortality (11%) and long-term survival. In summary, an infant rat paradigm of EEG-confirmed, hyperthermia-induced seizures which is suitable for long-term studies is described. This model should be highly valuable for studying the mechanisms and sequelae of febrile seizures.

Keywords

Febrile seizure; Animal model; Epilepsy; Hyperthermia; Infant; Rat; Development; EEG

1. Introduction

Febrile seizures are common, affecting 3–5 % of infants and young children [32,39]. Whether these seizures lead to neuronal injury or to subsequent epilepsy is controversial: prospective studies of children with febrile seizures have failed to reveal a progression to limbic (temporal lobe) epilepsy and its associated cell loss [8]. Conversely, populations of adults with temporal lobe epilepsy and evidence of limbic neuronal death (mesial temporal sclerosis), have a high prevalence (30–50%) of prolonged febrile seizures in childhood [10,13]. These data are difficult to reconcile [36]. Obvious concerns are, for example, whether the neuronal loss found in adults with a history of recurrent or prolonged febrile seizures was actually present prior to these seizures. In other words, whether a genetic or

acquired ‘lesion’ preceded and triggered both the febrile seizures and the subsequent temporal lobe epilepsy [32,38].

These fundamental issues of developmental epilepsy are difficult to study in the human but may be resolved using animal models [17,19]. Therefore, several groups have proposed animal models of febrile seizures. Holtzman et al. [18,28,29] studied 5–6-day-old rats, using a paradigm that was lethal to 10-day-old and older rats, and unsuitable for long-term studies. Further, only sparse and exclusively cortical EEG data were presented. The model presented by these authors did have the pharmacological pattern seen in human febrile seizures: phenobarbital, diazepam and valproate increased the threshold temperature for hyperthermic seizures, while phenytoin did not [29]. A rat model using microwave heating was described by Hjeresen and Diaz [16], to demonstrate the rapid decrease in susceptibility to hyperthermia-induced seizures occurring between the 10th and 17th postnatal days.

Morimoto et al. [23–26] developed a rat model with EEG-confirmed seizures, using heated air. However, these authors studied ‘juvenile’ rats on postnatal days 24–29, an age that is significantly older than that considered to correspond to human infants [11]. Further, these older rats were much more resistant to febrile seizures than younger rats [16], and developed behavioral seizures only when their core temperatures reached 44°C [24]. In a different paradigm, enhancement by hyperthermia of seizures and neuronal loss induced by kainic acid in adult rats has also been reported [22].

The goals of the study reported here were first, to determine the optimal age and parameters for hyperthermia-induced seizures in neonatal and infant rats. A second goal was to establish a reliable, reproducible model of febrile seizures with little mortality and morbidity, which would permit prospective long-term studies of these seizures.

2. Materials and methods

2.1. Animals

Rat pups were products of timed-pregnant Sprague-Dawley-derived rats that were obtained from Zivic-Miller (Zelienople, PA). Mothers were kept on a 12-h light/dark schedule and given access to unlimited lab chow and water [2,7]. Time of birth of pups was determined every 12-h, and the day of birth was considered day 0. Litters were culled to 12 pups on the first postnatal day, and kept in quiet, uncrowded AALAC approved facilities at a room temperature of 21–22°C. Overall, 155 rat pups participated in the study, and were divided into experimental groups as described below.

2.2. Experimental design

2.2.1. General set-up of the hyperthermia induction paradigm—Core temperature in this paradigm was raised using a regulated stream of moderately heated air that was directed to the top of a large (3 liter) glass container which served as a hyperthermia chamber. Baseline core (rectal) temperatures were measured (Thermistor probe; Omega engineering, Stamford, CT). Groups of three or four pups were then placed at the bottom of the glass container, and heated air (43.4–44°C) was blown into the top of the container (50 cm above the rats), using a commercial, adjustable hair dryer. Volume and temperature of the air were adjusted to increase core temperature at about 2 degrees per minute. Core temperature was measured every 2 min, and the behavior of the rats was continually monitored by two observers. The container was rinsed and dried between sessions of hyperthermia, so that the temperature of the chamber floor remained at ~ 20°C.

- i. For determination of the threshold temperature for hyperthermic seizures, core temperature was measured at the onset of the behavioral seizures in each rat, and the rat was then removed to a cool surface.
- ii. For induction of prolonged febrile seizures: when core temperature reached 41°C, the air-stream was adjusted with a goal of maintaining core temperature in the range of 40.5–42.5°C. Hyperthermia was induced for 30 min, and core temperature was measured every 2 min and at the onset of behavioral seizures. The number of seizures and the duration and characteristics of each one were noted at the same intervals. Pups with observed seizures were removed to a cool surface for 2 min, then returned to the hyperthermia chamber. Following the hyperthermia period, rats were monitored for an hour on a euthermic pad with temperature measurements every 15 min, then returned to home cages. A second option, which seemed to eliminate mortality (see below) was to remove the pups to a cool metal surface until their core temperature returned to base-line (32–33°C). They were kept on a euthermic pad for 30 min only, then returned to home cages.

2.2.2. Determination of threshold temperature and characterization of the behavioral seizures

—For determination of threshold temperature and characterization of the behavioral seizures, rats were studied on postnatal days 6–7 (12 each in the hyperthermia and control groups), postnatal days 8–9 (11 experimental and 6 control pups) or postnatal days 10–12 (22 experimental and 8 control animals). In each age group, control rats were exposed to a stream of non-heated air and maintained normothermic.

2.2.3. Determination of the electrographic correlates of the hyperthermic seizures

—For determination of the electrographic correlates of the hyperthermic seizures, 14 pups aged 10–11 days were implanted with electrodes for EEG recording. Bipolar electrodes (Plastics One, Roanoke, VA) were positioned as described in detail elsewhere [2–5,7]. Briefly, pups were subjected to halothane anesthesia and placed in an infant-rat stereotactic apparatus (Kopf Instruments, Tujunga, CA). Electrodes were implanted using age-appropriate coordinates [3], and were aimed at the frontoparietal cortex, basal amygdala and/or dorsal hippocampus. Each animal carried cortical and amygdala or cortical and hippocampus electrode arrays. EEGs were recorded using a GRASS apparatus from eight freely moving rats [3–5,7]. To eliminate the possibility of movement artifacts [4], EEGs were recorded also from restrained rats ($n = 6$).

2.2.4. The induction of prolonged or multiple hyperthermic seizures

—The induction of prolonged or multiple hyperthermic seizures was studied in 10–11-day-old rats. Eighty rats were divided into an experimental group ($n = 63$) which was exposed to 30 min of hyperthermia, and a control group ($n = 17$). Weight of pups and baseline and maximal core temperatures were recorded, and the latency to the onset of seizures and seizure duration were monitored. Mortality and the time of death with respect to the hyperthermia were noted.

All experiments were approved by the Institutional Animal Care and Use Committee, and were started between 08.00 and 10.00 h to avoid potential diurnal variability in seizure threshold.

3. Results

3.1. The optimal age and behavioral characteristics of hyperthermic seizures in the rat

In 6–7-day-old rats, the threshold temperatures for the onset of hyperthermia-induced seizures varied markedly among individual animals, as is evident from the large standard

error for this age group in Table 1. Moreover, the behavioral seizures at this age were not stereotyped. The hyperkinesia induced by the hyperthermia stopped either suddenly or gradually, and was followed by hypotonia or by tonic stiffening. Automatisms were sometimes observed.

The reliability and reproducibility of hyperthermia-induced seizures improved significantly by the 10th postnatal day. At this age, a uniform, abrupt, well-defined transition occurred between the running and random movement induced by the hyperthermia, and the onset of behavioral seizures. During a typical seizure, all movements stopped abruptly and the rat displayed tonic flexion, concurrently with biting and chewing of an extremity (usually a hind-limb). The tonic posture and rigidity persisted until the pup was removed from the hyperthermic chamber. Later in the course of the seizures, intermittent oral automatisms and wet dog shakes were frequent. Clonic movements or tonic extension were rarely, if ever, observed. In some rats who were maintained hyperthermic for 30 min, intermittent seizures extended beyond the hyperthermia period. These seizures also consisted of tonic flexion, oral automatisms and/or wet dog shakes.

3.2. The EEG features of hyperthermic seizures in the infant rat

The oral automatisms at the onset of seizures, which generally signify a limbic origin [15,27], suggested that EEGs should be recorded from the amygdala and hippocampus. Indeed, EEG confirmation of behavioral seizures was demonstrated in rats implanted with multiple bipolar electrodes aimed at these structures. In cortical recordings, only semi-rhythmic or sporadic spikes were seen. However, bipolar electrodes implanted in the amygdala and in the dorsal hippocampus revealed hyperthermia-induced rhythmic discharges concurrent with the onset of behavioral events. A typical EEG is shown in Fig. 1. During normothermia, both amygdala and cortical tracings typically revealed non-rhythmic, low-voltage discharges [4,31]. The onset of hyperthermic seizures was associated with alterations in the discharges recorded from the amygdala (and sometimes hippocampus): a flexion spasm (seen as a movement artifact in Fig. 1B, arrow) was followed by freezing without overt movements, except for oral automatisms. Concurrently, rhythmic discharges of progressively increasing amplitude were recorded in the amygdala leads (Fig. 1B,C). In the cortical recordings, a decrease in the abundance and the voltage of discharges was typical although, occasionally, no obvious change in cortical activity was evident.

3.3. Characteristics of the 30 min hyperthermia paradigm and the induced seizures in infant rats

Elevation of core temperatures of 10–11-day-old rats for 30 min resulted in hyperthermic seizures in 93.6% (Table 2). The maximal temperature averaged $42.3 \pm 0.1^\circ\text{C}$. A minority of rats (four of 63) who did not develop seizures did not differ in basal temperature ($33.1 \pm 0.7^\circ\text{C}$) or in maximal temperature achieved ($42.8 \pm 0.7^\circ\text{C}$) from those who developed seizures. The mean time to the onset of seizures was 4.4 min after the initiation of hyperthermia (Table 2). Seizure duration averaged 13.7 ± 0.8 min. Since the rats typically had 1–2 seizure episodes during the 30 min period of hyperthermia, the value for seizure duration reflects the cumulative time engaged in behavioral seizures.

3.4. Mortality of the hyperthermic seizure paradigm

Mortality was not encountered during the experiments evaluating the threshold temperature for hyperthermic seizures. This is likely due to the design of these experiments: the pups were removed to a cool surface within seconds of the onset of seizures. Therefore, mortality data is limited to the 10–11-day-old group subjected to 30 min of hyperthermia. Seven of 63 rats in the experimental group (11%) died. The duration of hyperthermic seizures was similar in rats who expired (12.8 ± 1.2 min) and in those who survived (13.9 ± 1.0 min). The

maximal core temperature recorded in pups who died ($43.0 \pm 0.23^{\circ}\text{C}$, $n = 7$) was slightly but significantly higher than the maximal core temperature of survivors ($42.3 \pm 0.11^{\circ}\text{C}$; $n = 56$; $P = 0.047$, unpaired Student's *t*-test). No pup expired during the hyperthermia period. Time of death ranged from 70 to 257 min after termination of the hyperthermia (mean: 155 ± 28 min). Deaths occurred in pups who were returned to home cages an hour or longer after the hyperthermia. Modification of the protocol by returning the pups to their mothers after a 30 min recuperation period eliminated mortality, presumably by permitting rapid rehydration of the rats.

4. Discussion

A paradigm of hyperthermia is described, which results in seizures in the large majority of immature rats with relatively low mortality. The seizures are induced most reliably and are most stereotyped in the 10–11-day-old rat, with a threshold temperature (Table 1) that permits prolonged survival. Furthermore, after several minutes of exposure to moderate hyperthermia, seizures are induced in the large majority of animals at a lower temperature (Table 2). The induction of seizures in over 90% of pups in this paradigm, as compared to other models [14,18] may be due to the relatively rapid elevation of core temperature [16]. Alternatively, the mildly heated air used in this paradigm permits a more prolonged exposure to sustained hyperthermia than was possible with other models [14], thus promoting hyperthermic seizures. The notion that sustained hyperthermia may promote seizures is supported by the fact that seizures did not occur instantaneously, but with a latency of over 4 min. Some previously reported models were lethal even on shorter exposures [14].

Besides reliability and reproducibility (i.e., seizure development in most animals), this model offers several advantages over previous reports. First, it relies on rats of appropriate age. In the human, febrile seizures are seen almost exclusively in infants (not neonates) and young children [8,39]. The susceptibility to the convulsant effects of hyperthermia decreases dramatically with age in the human [12]. In the rat, a major decline in the susceptibility to hyperthermic seizures is evident between the 11th and the 17th day of life [16]. Although precise correlations of rat and human brain development may be difficult, evidence based on the rates of brain growth and myelination suggests that the 5–7-day-old rat may be 'equivalent' to the human newborn [11]. Rat brain development during the period of 10–15 postnatal days best corresponds to the stage of brain development at which human infants are most susceptible to febrile seizures [11,16].

In addition, it is questionable whether results derived from older experimental animals can be extrapolated to mechanisms of febrile seizure generation in the 'infant' organism or to the sequelae of these seizures. For example, pronounced cell loss in the hippocampus (e.g., CA1, and CA3), amygdala, and piriform and entorhinal cortex is found in adult animals in whom prolonged seizures were induced by kainic acid, pilocarpine, etc [27]. However, during the second postnatal week, limbic neurons are resistant to excitotoxicity induced by any of these convulsants [27,34,35]. The reason for this fact is not entirely clear, but may relate to immature limbic circuitry during this developmental period, limiting the release of — or the response to — excitotoxins at target neurons [30,37]. Since the mechanisms leading to generation and consequences of febrile seizures may be age-dependent, an appropriate model of hyperthermic seizures should study 'infant' rats [6,27,33].

The febrile seizures in this model are confirmed by EEG. The behaviors induced by hyperthermia in the infant rat, uncontrollable biting and tonic stiffening, are similar to those observed after the administration of known convulsants [1,2,15]. However, it may be argued that these behaviors are not seizures, but postures induced by hyperthermia. In humans, EEG

correlations of genuine febrile seizures are rare since the seizures occur unexpectedly, and ethical reasons prohibit their provocation. A single case occurred in an EEG lab [24], and was recorded.

Previous age-appropriate models have lacked adequate EEG confirmation. Because the behaviors induced by hyperthermia in the current model were consistent with a limbic origin [3,15,27], EEGs were recorded from the amygdala and hippocampus. Moreover, cortical maturation is incomplete during the second postnatal week in the rat, resulting in poorly organized and low-voltage cortical EEG activity [4,31]. Nevertheless, published studies of infant rat hyperthermic seizures have lacked EEG data [9,16,20,21] or have documented only low voltage, semi-rhythmic cortical EEG ([28], in the five-day-old rat).

Models using age-inappropriate (older) rats have described cortical EEG only. Morimoto et al. [23–25] recorded cortical EEG from 24-day-old and older rats, and suggested that hyperthermic seizures originated from the occipital cortex. This is problematic for two reasons: first, the behavioral seizures reported are typical of limbic origin [1,3,15] and not of occipital seizures. Second, seizure propagation mechanisms may differ markedly in the mature and infant rat, making a direct application of Morimoto's data to the infant brain difficult (see above). In the model defined here, EEG was recorded both from cortex and from limbic subcortical regions, and demonstrated epileptiform discharges coincidentally with the behavioral seizures only in the amygdala and hippocampus.

An additional advantage of this model is its low mortality and suitability for long-term studies. The model was relatively free of the mortality and morbidity, including the confounding effects (and ethical issues) of burns, infection, etc, associated with other models. This fact also renders the current paradigm more analogous to the human situation of febrile seizures, in which mortality is practically non-existent. Early reported paradigms utilized a heated copper sheet as a heat source, resulting in burns (Holtzman, personal communication). Microwave heating has been used for increasing core temperature [16], but unrelated short- and long-term effects of microwaves on neuronal function cannot be excluded. The use of warm air in our hands has resulted in minimal morbidity (reddening of ears and paws) and low mortality.

The paradigm presented here does not require a costly apparatus, and is suitable for a variety of experimental uses. For example, a known effect of some anticonvulsants, such as barbiturates and valproate, is to elevate the threshold temperature at which seizures develop [29]. These drugs, as opposed to phenytoin which does not elevate threshold temperature, are effective in the prevention of human febrile seizures. Thus, the current model can be used to screen agents for potential efficacy for febrile seizures.

In conclusion, a model of hyperthermic seizures is described, which uses animals of appropriate age, results in reproducible seizures in the majority of animals, possesses EEG correlates, and is suitable for long-term studies. Therefore, this paradigm should prove highly valuable for studies of the fundamental issues in human febrile seizures, such as their mechanisms and long-term outcome.

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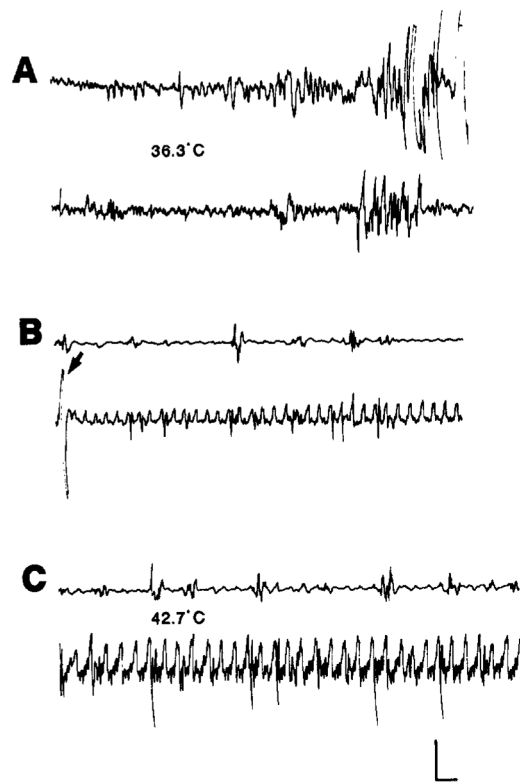


Fig. 1.

EEG correlates of febrile seizures in a 10-day-old rat. Electroencephalogram was obtained as described in the text. The top tracing of each panel is cortical, and the bottom tracing was recorded from a bipolar amygdala electrode. A, recorded at core temperature of 36.3°C, shows non-rhythmic waves and a movement artefact. As the hyperthermia progressed, B shows the onset of a behavioral seizure: the arrow points to a movement artifact associated with the severe tonic flexion. Rhythmic discharges of increasing amplitude are seen in the amygdala lead, while cortical activity is minimal. In C, seconds later, core temperature has been determined. Epileptic discharges are seen in the amygdala lead, while the cortical EEG shows only discrete, non-rhythmic discharges on a 'flattened' background. Vertical scale is 50/ μ V, horizontal scale is 1 s.

Table 1

Effect of age on threshold temperature and phenotype of hyperthermic seizures

Age (day)	<i>n</i>	Threshold temperature	Observed behaviors
6–7	12	40.9 ± 0.8	Variable: hypotonia or stiffening, rare automatisms.
8–9	11	41.6 ± 0.3	Behavior-arrest with biting, chewing or hypotonia.
10–12	30	42.7 ± 0.2	Stereotyped: tonic flexion with biting, chewing.

Core (rectal temperatures) are given in °C; see text for the threshold temperature evaluation paradigm. Values are means ± S.E.M. The means of each group are significantly different ($P = 0.034$, Kruskal-Wallis non-parametric ANOVA). The S.E. of the 6–7-day-old group is significantly larger than that of the other groups.

Table 2

Parameters of the sustained hyperthermia and hyperthermic seizures

Experimental group	Hyperthermia (<i>n</i> = 63)	Controls (<i>n</i> = 17)
Baseline temperature (°C)	32.8±0.1	33.1 ±0.3 ^a
Maximal temperature	42.3 ± 0.1	Not applicable
Percent with seizures	93.6 (59/63)	0
Seizure latency (rain) ^b	4.4 ± 0.4	Not applicable
Seizure duration (min) ^b	13.7 ± 0.8	Not applicable
Mortality (%)	7/63 (11)	0

^a $p > 0.05$ compared with the experimental group.

^b In the rats who had seizures.